Cell Cycle

I. Cell Cycle Overview

A. Cellular Division

1. Required during development to produce a functioning organism

2. Replaces cells throughout life

3. Dysfunction can lead to various cancers

II. Phases of the Cell Cycle

A. Gap1 (G1) Phase

1. Cell volume returns to normal and genetic material returns to diploid

2. Metabolism of biomolecules required for DNA replication

3. Cells can withdraw from G1 phase and become senescent in G0 phase

B. S(ynthetic) Phase

1. Replication of nuclear DNA

2. Following S phase, cells contain tetraploid (4n) number of chromosomes

3. Mechanisms are in place to ensure replication only occurs once

C. G2 Phase

1. Metabolism of molecules required for mitosis

2. DNA is analyzed for possible errors and they are corrected

3. Cell has two pairs of chromosomes at this point

D. Mitosis

1. Following interphase, cell division

2. Occurs at the conclusion of G2

III. Mitosis

A. Prophase

1. Chromosomes begin to condense (but not quite apparent)

2. Mitotic spindle begins to form

3. Kinetochore is formed in preparation for migration

B. Pro-metaphase

1. Nuclear envelope breaks down

a. Due to phosphorylation of lamins

2. Chromosomes have condensed and are in a random arrangement

C. Metaphase

1. Chromosomes line up on the metaphase plate

D. Anaphase

1. Sister chromatids separate and move to the poles

E. Telophase

1. Two sets of daughter chromosomes arrive at the poles

2. Contractile ring begins to form

F. Cytokinesis

1. Formation of the cleavage furrow

2. Cytoplasm and cell membrane is pinched in half

3. Results in two daughter cells

G. Endoreplication

1. Cell undergoes the normal stages of interphase, but not mitosis

2. Results in one large cell with multiple sets of chromosomes (polyploidy)

a. Liver cells and megakaryocytes are polyploids

b. Polyploidy is also present in cancer – due to aberrant processes

IV. Cell Cycle Regulation

A. Checkpoints

1. Ensure that conditions are favorable for cell cycle progression

2. Restriction Point

a. Occurs during G1 phase

b. Point of no return – after passing the cell will enter S phase

B. Cell Fusion Experiments

1. Used to identify cell cycle inducers

2. Two cells at different points of the cell cycle are fused

a. S-phase cells can induce G1 phase cells to replication

b. M-phase cells can induce cells to divide (MPF)

c. G1 does not have any inducing factors

C. Cyclin Dependent Kinases (CDKs)

1. Kinases that requires cyclins to be present for activity

2. CDK levels are constant throughout the cell cycle

a. Activity is regulated by changes in the levels of cyclin

3. Positive regulators of the cell cycle

4. Activated by Cdk-activating kinase (CAK) through phosphorylation

a. Phosphorylation site exposed only after binding to cyclin

5. Proteolysis of cyclin following mitosis inactivates CDK

a. Cyclins contain an AA sequence that is targeted for ubiquitination

b. Ubiquitinated cyclin is sent to proteasome for degradation

6. E2F

a. Transcription factor that activates expression of cyclin genes

b. Activation of E2F is a positive input for the cell cycle

7. Multiple CDKs and cyclins regulate passage of mammalian cells through cell cycle

8. Cyclin-CDK complexes regulate cell cycle by phosphorylating target proteins

a. M-CDK

i. Histones – condensation of chromatin

ii. Lamins – breakdown of nuclear envelope

b. G1-CDK

i. Rb – Decouples from E2F

V. Negative Regulation of Cell Cycle

A. Retinoblastoma (Rb) protein acts as a brake in G1 cells

1. Transcription of S-phase genes is activated by E2F

2. Rb normally complexes with E2F, keeping it inactive

3. CDK phosphorylated Rb, removing it from E2F

a. Allows S-phase gene transcription to occur with E2F

B. CDK Inhibitors (CKIs)

1. CKIs inactivate CDK-cyclin complexes and prevent Rb phosphorylation

2. Two families:

a. INK4 family

b. KIP family: inhibits all G1 and S phase CDK complexes

3. Bind to CDK-cyclin complexes and change the conformation, inactivating complex

C. p53

1. Sensor that arrests cells with damaged DNA in G1

2. Activated p53 can promote cell cycle arrest, apoptosis, and DNA repair

3. p53 is a transcription factor for p21, a CKI

a. Upon DNA damage, p53 levels are increased, increasing p21 transcription

b. Results in inactivation of CDKs and cell cycle arrest

4. Normally complexed with MDM2, but is phosphorylated follow DNA damage

a. Phosphorylation causes it to dissociate from MDM2

VI. The Cell Cycle and Cancer

A. Cancer cells are defined by two heritable properties

1. Overproliferation

2. Metastasis

B. Causes of overproliferation

1. Rb and p53 act as tumor suppressors 🡪 loss of them may cause cancer

a. Both are guardians of the G1-S interphase

2. Viral products may block function of p53 and Rb, leading to cancer

a. Genetic mutations aren’t always necessary

C. Retinoblastoma – caused by loss of both Rb alleles

1. Loss of 1 will have no phenotype, but designated carrier

2. Carriers may sporadically lose the 2nd copy, causing tumor

3. In most cases both copies of Rb are sporadically inactivated

D. Hereditary Melanoma

1. Linked to disruption of p16

2. p16 acts as a checkpoint when there is DNA damage

a. Cells become senescent, stop cell cycle, and age

3. p16 helps keep cancers in check, but levels must be carefully regulated

a. High levels of p16 will prevent tissues from regenerating

E. p53 and Tumorigenesis

1. Most commonly mutated gene in cancer

2. Acts as a tumor suppressing by stopping cell cycle in cells with DNA damage

3. Li-Fraumeni syndrome

a. Rare syndrome where patients have a variety of cancers at an early age

b. Caused by mutations in p53

F. Cancer Drug Therapies

1. Alkaloids – block formation of MT spindle in M-phase

2. Antitumor Antibiotics – cause DNA damage and induce cell death in S-phase

3. Antimetabolites – interfere with S phase

4. CDK-Inhibitors – can block all stages by blocking CDK-cyclin complexes

5. Drugs can exert their toxic effects on cancer cells at several points in the cycle